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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/463,320 | 01/22/2000 | TONY PELED | 1194/7 | 6181 |

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

| EXAMINER |
|---|
| BELYAVSKYI, MICHAIL A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | 26 |

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/463,320 | PELED ET AL. | |
| | Examiner | Art Unit | |
| | Michail A Belyavskyi | 1644 | |

*-- The MAILING DATE of this communication appears n the c ver sheet with the c rrespondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-13,15,37-45 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-13,15,37-45 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05/11/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 06/11/03 (Paper No. 25), is acknowledged.

Claims 1-2, 4-13, 15, 37-45 and 47 are pending.

*Claims 1-2, 4-13, 15, 37-45 and 47 as they all read on the elected species wherein neonatal umbilical cord blood is species of specific hematopoietic cells , tetraethylenepentamine (TEPA) is specific transition metal chelator, stem cell factor and GM-CSF is specific early and late acting cytokine are under consideration in the instant application.*

In view of the amendment, filed 06/11/03 (Paper No. 25), the following rejections remain

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

Claims 1-2, 4-13, 15, 37-45 and 47 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing CD4+ ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells does not reasonably provide **enablement** for a method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing *any hematopoietic* cells ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population enriched for CD34+ cells, while at the same time inhibiting differentiation of said cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, Paper No: 21, mailed 02/11/03.

Applicant's arguments, filed 06/11/03 (Paper No. 25) have been fully considered, but have not been found convincing.

Applicant asserts that claims 1 and 37 have been amended to recite that the hematopoietic cells expanded ex vivo are enriched for CD34+ cells and that " the examiner acknowledges that hematopoietic cells enriched for CD34+ cells are enabled".

Contrary to Applicant's assertions, in the previous Office Action the Examiner acknowledges that the specification only discloses that providing $CD4^+$ cells *ex-vivo* with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, only $CD4^+$ cells expanding and at the same time inhibiting differentiation (see examples 1 and 2 in particular). The Specification disclosed that CD34+cells were first selected from peripheral blood cells with murine monoclonal anti CD34 antibody and then this CD34+ cells , not *any hematopoietic* cells , were expanded *ex vivo* . In other words, the Examiner acknowledges that the specification only provide enablement for CD34+ cells that were first isolated ( i.e. enriched) and then used for *ex vivo* expanding , not for *any hematopoietic* cells that were provided *ex vivo* with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population enriched for CD34+ cells.

The specification does not adequately teach how to effectively expand and at the same time inhibit differentiation of *any hematopoietic* cells by providing said cells ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper.

The specification does not teach how to extrapolate data obtained from $CD4^+$ cells *ex-vivo* assay studies to the development of effective protocols for imposing proliferation and at the same time restricting differentiation of *any* stem or progenitor cells by culturing said cells under conditions that reduces the capacity of said cells in utilizing copper. Moreover, Applicant himself acknowledge that the mechanism of the effects of cupper is unknown (see page 3, line 35-37 in particular). As such, the invention must be considered unpredictable. In addition, Percival ( Am .J. Clin. Nutr. 1998, Vol.67 p.1064-1068) teaches that the role of copper in effecting cellular function is contradictory and that more studies have to be done to understand the mechanisms by which copper effect the process of differentiation in various types of cells (see entire document, pages 1064 and 1066 in particular).

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing *any hematopoietic* cells ex-vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-2, 4-5, 8-13, 15, 37 , 40-45 and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al( Blood Cells, 1994, v.20, pages 468-481) or C.De Bruyn et al., ( Stem Cells 1995, v.13, pages 281-288) each in view of Cicuttine et al (Blood, 1992, v 80, pp 102-112) for the same reasons set forth in the previous Office Action, Paper No: 21, mailed 02/11/03.

Applicant's arguments, filed 06/11/03 (Paper No. 25) have been fully considered, but have not been found convincing.

Applicant asserts that: (i) neither Moore nor De Bruyn teach or suggest reducing the capacity of the hematopoietic cells in utilizing copper to inhibit differentiation during ex-vivo expantion; (ii) Cicuttine et al., does not teach that reduction of copper is useful for ex vivo expansion of hematopoietic cells.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

Moore et al. teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient ( see, entire document, abstract in particular). Moore et al. teach that the hematopoietic stem cells can be derived from umbilical cord blood (see page 469 in particular). Moore et al. teach a growth medium with nutrients and early and late acting cytokines (See Material and Methods in particular). Moore et al. teach that ex vivo expansion of cord blood CD34+/CD38- cells will permit improved engraftment of adults ( see abstract in particular).

Similarly, C.De Bruyn et al. teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining $CD34^+$ hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient ( see, entire document, abstract in particular) C.De Bruyn et al. teach that the hematopoietic stem cells can be derived from umbilical cord blood or from bone marrow (see Page 282, in particular). Moore et al. teach a growth medium with nutrients and early and late acting cytokines (See Material and Methods in particular).

Moore et al. or C.De Bruyn et al. does not explicitly teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, under define growth conditions for reducing a capacity of hematopoietic cells in utilizing copper that will stimulate growth while inhibit differentiation .

Cicuttine et al. teach a method of coculturing hematopietic progenitor cells using define growth condition that will stimulate growth while inhibit differentiation ( see entire document, page 104, column 2 in particular). The growth media containing nutrients, early and late acting cytokines and zinc. As taught by Cicuttine et al. ( see Discussion in particular) zinc has an affinity to copper and thus would reduce copper utilization of culturing hematopoietic cells. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made that culturing the cell in the medium containing zinc would reduce a capacity of hematopoietic cells in utilizing cooper, absent a showing of unobvious property.

It appears that applicant and the examiner differ on interpretation of both the claimed method and the prior art. It is the examiner position that Cicuttine et al. teach the method that will result in the growth of hematopoietic cells , not stromal cells as suggested by Applicant, while inhibiting differentiation.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Cicuttine et al. to those of Moore et al. or C.De Bruyn et al. to obtain a claimed method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising the steps of culturing cells ex vivo under define growth conditions for reducing a capacity of hematopoietic cells in utilizing copper, using media containing zinc, which will reduce a capacity of culturing cells in utilizing copper, thereby stimulate cell proliferation while inhibiting differentiation of said cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because cultivating cells under growth conditions for reducing a capacity in utilizing copper using zinc containing medium will support only growth, proliferation and expansion without inducing differentiation of said cells as taught by Cicuttine et al. that can be further used a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient as taught by Moore et al. or C.De Bruyn et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

5. Claims 6-7 and 38-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al( Blood Cells, 1994, v.20, pages 468-481) or C.De Bruyn et al., ( Stem Cells 1995, v.13, pages 281-288) each in view of Percival et al (J Nutrition, 1922, v122 pages 2424-2429) for the same reasons set forth in the previous Office Action, Paper No: 21, mailed 02/11/03.

Applicant's arguments, filed 06/11/03 (Paper No. 25) have been fully considered, but have not been found convincing.

Applicant asserts that Percival et al does not cure the fatal deficiencies of Moore and De Bruyan. Applicant asserts that : (i) HL-60 is a cell line that could not be isolated from a donor or patient as the claims require; (ii) no conditions that stimulate growth or inhibit differentiation could be provided to a leukaemic cell line such as HL-60, because HL-60 are tumor cells which proliferate and do not differentiate.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

Moore et al. or C.De Bruyn et al. does not explicitly teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, under define growth conditions for reducing a capacity of hematopoietic cells in utilizing cooper, using a tetraethylenepentamine as a transition metal chelator.

Percival et al. teach culturing condition using define growth medium condition that will stimulate growth while inhibit differentiation. ( see entire document, Abstract in particular). Moreover, Applicant acknowledge that Percival et al. teach that cells can be made copper deficient by incubating them in the media containing tetraethylenepentamine without loss of viability or alteration in the stage of differentiation ( see page 13 of Applicant's arguments, filed 06/11/03 , Paper No. 25 in particular). This supports the examiner position that TEPA support proliferation while inhibiting differentiation.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Percival et al. to those of Moore et al. or C.De Bruyn et al. to obtain a claimed method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising the steps of culturing cells ex vivo under define growth conditions for reducing a capacity of hematopoietic cells in utilizing copper, using a tetraethylenepentamine as a transition metal chelator, thereby stimulate cell proliferation while inhibiting differentiation of said cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because cultivating cells under growth conditions for reducing a capacity in utilizing cooper using a tetraethylenepentamine as a transition metal chelator, will support only growth, proliferation and expansion without inducing differentiation of said cells as taught by Percival et al., that can be further used a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient as taught by Moore et al. or C.De Bruyn et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. No claim allowed

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
August 5, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600